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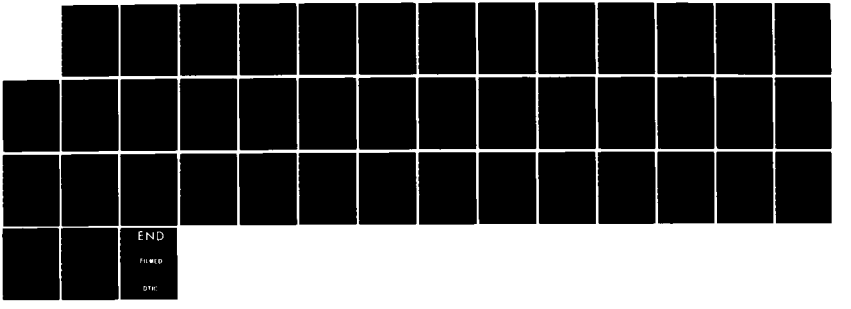

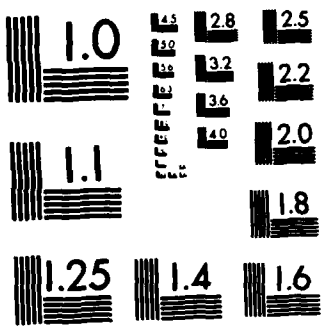

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THE PHYSIOLOGY OF ULTRADIAN RHYTHMS AND THEIR ROLE IN AFFECTING DISEASE RESISTANCE

Final Report

Benjamin H. Natelson, M.D.

Walter N. Tapp, Ph.D.

October 1, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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United States military combat personnel will not always be able to maintain normal 24 hr schedules of work and rest. Our laboratory has been studying in what ways biological rhythms interact with some non-standard light-dark schedules to affect how well an animal functions and how susceptible it is to disease. Contrary to what might be expected, we have found that a number of non-24 hr schedules actually protect rodents from

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both stress-induced and spontaneously occurring diseases. This phenomenon, which we call "chronotherapy," may eventually be used to reduce the incidence of disease in stressful situations where the length of the light-dark schedule can be controlled, such as in spacecraft. We hypothesize that these non-standard light-dark schedules enhance disease resistance by changing the relationships between various behavioral and physiological rhythms. To examine the relationships between rhythms in animals on non-24 hr schedules, we have developed a system which concurrently monitors behavior (motor activity; performance on a vigilance-choice task, feeding) and physiological processes (plasma cortisol; core temperature) in non-human primates. Using this model, we have found that the usual notion of what consitutes entrainment is somewhat inaccurate. In contrast to what we had expected, we found that different variables were composed of biological rhythms of different frequencies. Temperature was the least variable with a well entrained 24 hr period. Activity, on the other hand, was much more variable with onsets sometimes occurring before lights on and other times following it. Some responsibility for this variability could be attributed to a superimposed low frequency rhythm (period over 30 hr) which free ran through the 24 hr rhythm. Of interest was the fact that in all rhythms studied, despite the variability in power at circadian periods, remarkable consistency was found in power at the ultradian periods (i.e., 40 and 80 min). This suggests an important relation between ultradian and circadian rhythms.

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FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

BACKGROUND

By now, it is widely acknowledged that our bodies march to the beat of a circadian drummer. However, we do not understand much about the interplay between the body's temporal arrangements and its overall function, health, and vigor. For example, removing putative pacemaker structures (the rodent SCN, the sparrow pineal, the cockroach optic lobes) abolishes coherent circadian rhythms (see Menaker et al., 1978 for review), but has no obvious effects on the animal's health or general well-being. In contrast, procedures which disturb the internal temporal order in animals that have intact rhythms have been reported to have harmful effects on health, performance, and longevity. These reports seem to derive from three basic models which we shall call the jet lag model, the shift work model, and the resonance model. While these models are often taken to be essentially equivalent we shall see that there are important differences between them.

The conceptual theme linking all of these models is the idea that a multicellular organism constitutes an ensemble of circadian oscillators with particular phase and frequency relationships that describe the organism's internal temporal organization. Presumably, normal temporal organization is comprised of the internal phase and frequency relationships imposed on the organism by entrainment to normal 24 hr days. Phase shifts or non-24 hr days alter the entraining stimuli and produce changes in internal phase and frequency relationships known as internal desynchrony. The harmful effects reported in the jet lag studies, the shift work studies, and the resonance experiments are all commonly attributed to changes in internal temporal organization during internal desynchrony.

Unfortunately, our present understanding permits only the crudest characterization of concepts such as internal desynchrony or internal temporal organization. To speak generally of "internal synchrony" or "normal internal temporal organization" suggests that all of the creatures under the sun have the same internal organization regardless of whether they are young or old or healthy or feeble. This seems unlikely. It seems likely that at least one necessary step towards understanding the relationship between internal temporal organization, health, and performance will be to begin to adequately describe internal temporal organization.

The most familiar of these three models is undoubtedly the jet lag model. Jet lag is a syndrome associated with phase shifting the circadian rhythm abruptly to a new schedule (e.g. a different time zone). The jet lag syndrome familiar to transmeridian travellers is characterized by fatigue, dysphoria, impaired psychomotor performance (Hauty & Adams, 1966a,b; Klein & Wegmann, 1974, Taub & Berger, 1974), and frank amnesia in animals (Tapp & Holloway, 1981). The deleterious effects of phase shifting typically have been ascribed to the transient internal desynchronization that occurs because different circadian rhythms shift from old phase to new phase at different rates (Hauty & Adams, 1966a,b; Higgins et al., 1976). However, this attribution is tenuous at best, because there is little direct evidence linking the changes in circadian order with functional changes.

The observation that single phase shifts degrade health and performance

leads one to ask if there is a cumulative hazard when an organism is exposed to repeated phase shifts. This is an important question because rotating shift workers experience just such repeated phase shifts. Unfortunately, it is not a question with a simple answer. Shift workers appear to have a higher incidence of accidents, self-reported health complaints, and lower job satisfaction than nonrotators (Czeisler et al., 1982). However, the increase in accidents may be due in part to sleepiness, a major complaint of the shift workers in the study, and disturbances in the workers' social lives may have contributed to job dissatisfaction.

Attempts to examine the effects of repeated phase shifts on health and disease have been even more equivocal. In a review of much of the shift work literature, Akerstedt (1976) found that shift workers had the same mortality rate as day workers, and many of the health problems reported by shift workers were largely restricted to the night work period or were transitory. Similarly, some studies report increased gastrointestinal disturbances in shift workers, but other well-executed studies have not found this increase. Animal studies have yielded equally inconsistent results. Aschoff et al. (1971) found that repeated 6 hr phase shifts decreased the lifespan of blowflies. However, in mice, repeated shifts only decreased longevity when they were initiated at one year of age and not when they were initiated at conception (Halberg et al., 1977). A similar, very well controlled study failed to find any overall changes in the lifespan of normal rats (Finger, 1982) as a result of repeated phase shifts carried out at different frequencies over different periods during the rats' lives. A final addition to this confusion is an interesting set of experiments by Hayes (1976). She has reported that some schedules of repeated phase shifts can increase longevity in insects. Together, these results seem to be resounding support for Halberg's (1976) contention that, "The effects of shift work can be good, bad or indifferent."

Regrettably, we cannot presently say whether any given schedule of repeated shifts will be helpful or harmful. One problem in thinking about these models has been the rather naive expectation that some number of phase shifts would produce some sort of additive extension of the effects of one phase shift. For example, Sekiguchi et al. (1976) have shown that rapid return to the old phase can minimize jet lag in man. Thus, appropriately spaced shifts (e.g. frequent 180^{0} shifts) may nullify rather than reinforce one another's effects. Indeed, once we abandon the simple cumulative model of repeated phase shift effects we find that the situation becomes enormously complicated to predict, depending at least on the direction, magnitude and frequency of the shifts, the strength of the entraining agent used to effect the shifts, the free-running period of the animal (which may be an indirect function of its age (Pittendrigh and Daan, 1976)), the phase of the rhythm at which shifts begin, and the animal's range of entrainment. Worse yet would be the problem of trying to follow the rhythms. In many of these schedules, one could expect rhythms to show long, nonmonotonic transients and other chaotic behaviors (Pittendrigh, 1974). Thus, although repeated phase shifts may have functional effects, the model seems too complicated to be useful.

The third model, the resonance model, avoids many of the problems associated with repeated phase shifts. Rather than presenting a phase change every few days, these experiments examine the effects of making the

body march to the beat of a non-circadian drummer. Thus, resonance experiments compare the effects of living in normal 24 hr days with the effects of living in non-24 hr schedules (such as 21 hr days or constant light) in the expectation that, through evolution, the organism is optimally suited to live in environments that cycle with a 24 hr period or a period that is close to its free-running period (Pittendrigh, 1974). The non-24 hr schedules used in these experiments are much more tractable than repeated phase shifts, because their effects on the rhythm are generally simpler to follow and because these schedules have been classic tools in the exploration of circadian phenomenology. Early data supporting this model were found in plants and insects (see Pittendrigh, 1974 for review). More recently, Saint Paul and Aschoff reported that blowflies living in 24 hr days (LD 12:12) lived longer than flies living in constant light, 20 hr days (LD 10:10) or 28 hr days (LD 14:14). However, flies living in 26 hr days (LD 13:13) lived longer than flies living in 24 hr days. The authors suggested that this might be because the free-running period of the blowfly was closer to 26 hr than to 24 hr. Subsequent evidence showing that the blowfly's free-running period averages 25.1 hr in constant light (over 2 - 1400 lux) seems indeterminate on this point. Recently, Fuller et al. (1978) reported that living in constant light impaired homeostatic thermoregulation in squirrel monkeys, and this effect seemed to be associated with internal circadian desynchrony. However, it is not yet clear whether this physiological deficit has pathological consequences.

There are, however, a surprising number of exceptions to the suggestion that non-24 hr days have deleterious effects. For example, Lais et al., (1974) found that living in constant dark delayed the onset of hypertension in spontaneously hypertensive (SHR) rats. Similarly, an early study by Lobban (1960) showed that unacculturated Eskimos living in an arctic environment with poor LD time cues exhibited strongly damped or undetectable circadian rhythms. But there was no evidence to suggest that this circadian anomaly reduced the Eskimos' lifespan. Finally, over the last 30 years Wever and Aschoff have conducted a famous set of experiments on people living in non-24 hr days. The summary chapter of Wever's recent (1979) review of that work makes fascinating reading. Contrary to his expectations, Wever found that people showed better performance when they were internally desynchronized than when their circadian system was internally synchronized. Moreover, people reported feeling better during internal desynchrony, leading Wever to conclude that the subject, "is subjectively in a better state when the circadian system is in internal disorder than in its 'normal' state." This analysis remains generally unappreciated (e.g. Moore-Ede et al., 1982). So too is the apparent discrepancy noted in this review that internal desynchrony has been cited as the reason for diametrically opposite findings -- namely, that people do not feel well after acute phase shifts and feel better when living in non-24 hr day/night schedules. Our relative state of ignorance about this problem is due to the fact that the phenomenon of internal desynchrony has not been researched in adequate enough detail. We believe this viewpoint readies the reader to consider the work we have done in the past 2½ years.

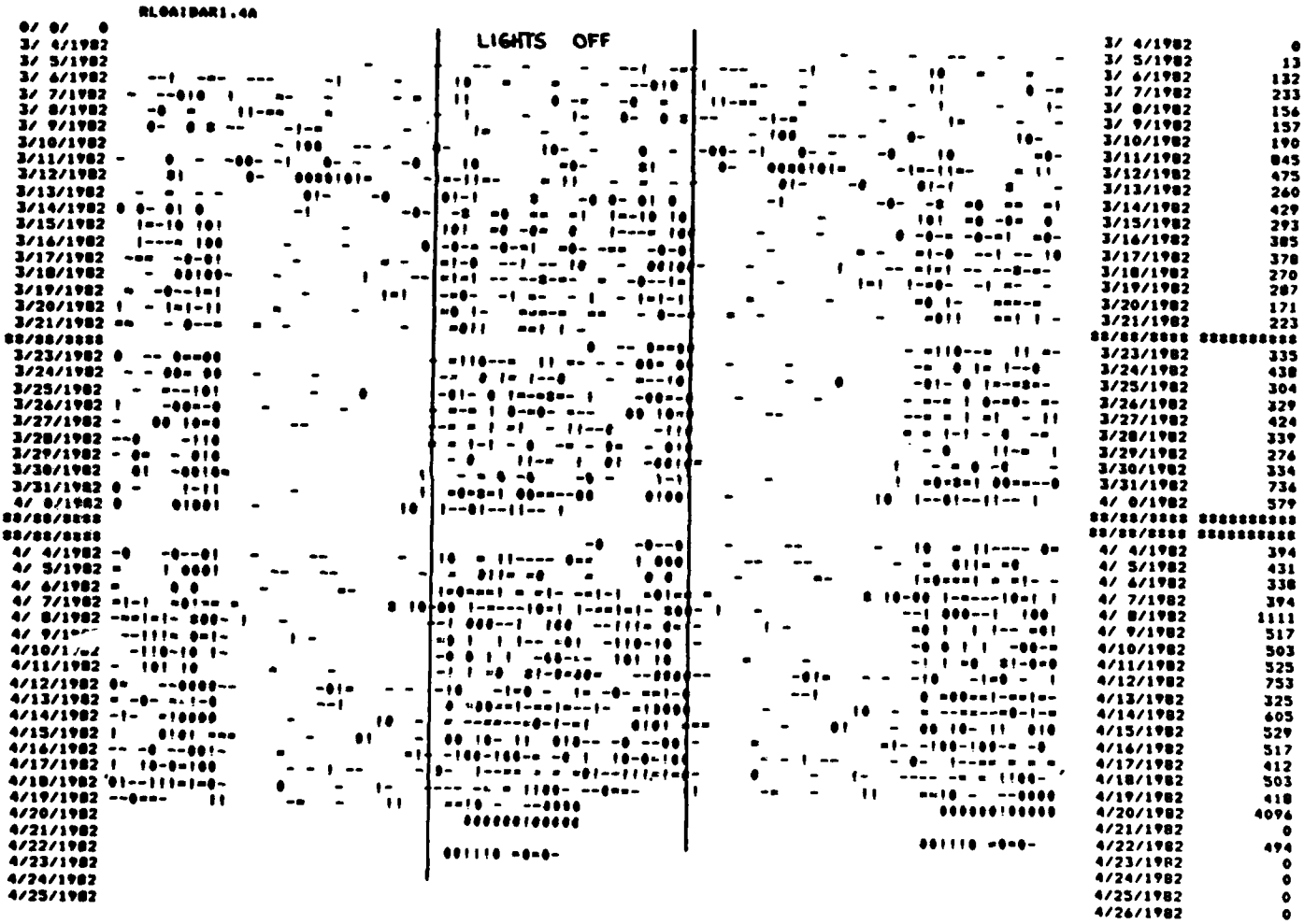
Resume of Work Accomplished to Date -- We have worked on 3 sets of experiments designed to investigate the functional effects of non-24 hr days on longevity, disease susceptibility, performance and biological rhythms. In the first of these, we sought to determine the effects of non-24 hr light-dark

(LD) schedules on 2 models of stress-induced disease in rats; these are immobilization induced gastric disease and "activity-stress" induced death. The second experiment was designed to look at the effect of one particular non-24 hr schedule (i.e., constant light [LL]) on resistance to spontaneous heart disease in hamsters (i.e., death due to an inherited cardiomyopathy). The final set of experiments was designed to study the effect of altered length LD schedules on fast frequency (i.e., ultradian) rhythms of the rhesus monkey. Variables to be studied included performance on a vigilance and on a choice task as well as a number of physiological parameters (i.e., core temperature, motor activity and plasma cortisol).

Stress Induced Disease and Non-24 Hr Schedules -- Cold-immobilization Model: Using cold immobilization as a stressor to produce acute gastric erosive disease, we proposed to contrast the disease resistance of rats living in constant light (LL) with that of rats living in a standard LD 12:12 environment. In our first experiment, we used groups of female rats that had lived in individual shoe-box cages in either LD or LL for 5 months. Because there is a circadian rhythm of susceptibility to gastric disease, one immediate concern was to be sure that the initiation of stress came at the same time in the animal's subjective "day" regardless of which light condition it had been placed. To do this, we provided rats with gnaw bars which were connected via relays to our computer. These data allowed us to monitor the animals' circadian activity rhythms. Figure 1 shows a teletype plot of the data from a typical rat living in LD. Days are plotted sequentially along the vertical axis. However, the record is double-plotted so that the left side of the plot is reproduced one line up on the right side. Thus, each line represents 48 hr of continuous data. This plotting convention aids visual inspection. Each symbol represents 30 min of accumulated activity, and our program allows for 4 different intensities of darkness where the darker shade indicates more behavior. Figure 2 shows the record from a typical rat exposed for a long time to constant light: As can be seen, the circadian rhythm has broken down and the animal displays an aperiodic pattern of behavior. In our model, the LD rats are stressed several hours before the onset of their active period. Because of the aperiodic nature of the LL rats' records, we stressed the rats at the same clock time as their LD mates. Seventeen hr after immobilization at 60° F, the rats were sacrificed and their stomachs quantified under a dissecting microscope for the length and number of gastric erosions. LL rats had significantly smaller gastric lesions (8 mm $\pm$ 6 SEM) than did LD rats (58 mm $\pm$ 13 SEM, $p<0.01$); the difference in lesion size between the two groups was not statistically significant (Tapp & Natelson, 1981). Thus, this experiment was important in showing that constant conditions could protect a rat from stress-induced gastric disease.

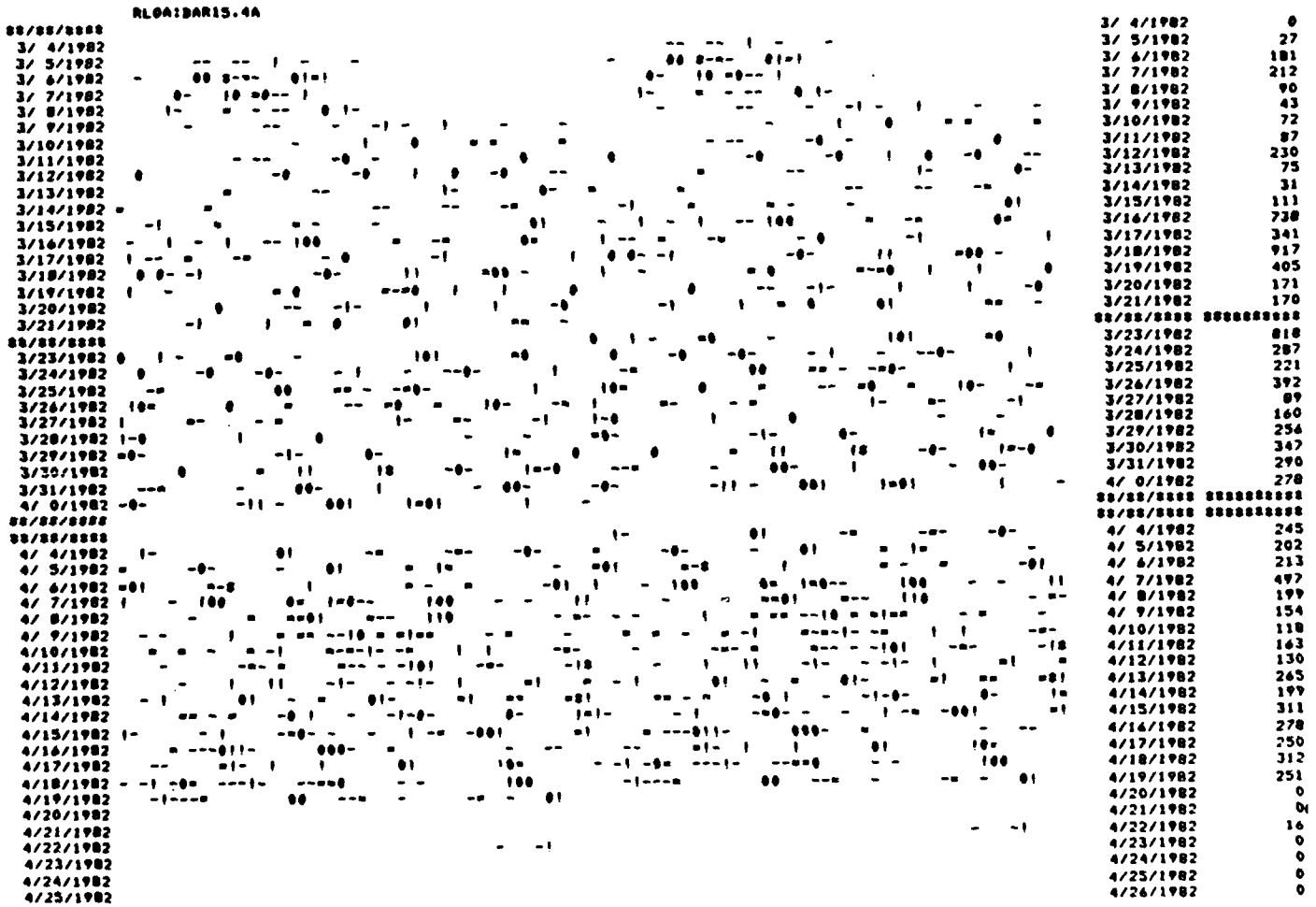
However an effort to replicate this experiment in another group of females yielded suggestive but not definitive results while other experiments in males were frankly negative. It became obvious to us that the immobilization-stress model produced very variable pathology. In other work, we learned that some of the sources of variability were seasonal change, prior stress history, gender and room temperature during restraint (Natelson et al., 1983). But even when these factors are controlled, it is difficult to get stable control data with this stress model. We believe the data indicate that the phenomenon is there but that the use of cold-immobilization -- with its many poorly understood physiological effects -- produces

FIG 1



DOUBLE PLOTTED TELETYPE (TTY) PLOT OF
LD RAT'S GNAWING BEHAVIOR

FIG 2



DOUBLE PLOTTED TELETYPE (TTY) PLOT

A RAT IN CONSTANT LIGHT (LL)

too much noise to show this subtle phenomenon clearly. Since we have been more successful with other animal models, we plan to deal with this problem in the work we subsequently will do by dropping cold-immobilization as a tool to explore the protective value of exposure to non-24 hr schedules.

Stress Induced Disease and Non-24 Hr Schedules -- Activity-Stress Model: Activity-stress was the second model we used to study the effects of non-24 hr days on disease. During activity-stress, rats are given 1 hr daily access to food and unlimited access to a running wheel. Over time, rats in this situation run more and more, eat less and less, develop a variety of pathologies and then die. The reasons for this "self-starvation" are not clear, but current evidence seems to implicate an interaction between the rat's ability to learn to eat a lot during its short period of food access and wired-in, species-typical behaviors such as activity in anticipation of feeding (Pare, personal communication). Regardless, we decided to use the syndrome because it had reliably lethal consequences and because the presence of a running wheel provided a natural opportunity to monitor circadian rhythms in non-24 hr days. In our first experiment, male rats, weighing 150-200 g, were adapted to Wahmann activity cages with unlimited access to food and water for 5 days. Half of the rats were put in LL and the rest in LD 12:12. After the fifth day, access to food was restricted to the period between 0900 and 1000 h. Figure 3 shows the results. Sixty-nine percent of the rats in LD 12:12 died while none of the rats in LL died.

Several potential explanations for the beneficial effects of LL can be excluded at this time. Increased survival in LL was not due to decreased running in LL rats. Prior to the onset of the burst of activity associated with the terminal stages of activity-stress, rats living in LL ran as much per unit time as rats that died in LD. In fact, the survivors in LD ran significantly less than the survivors in LL ($p<0.01$), with some animals in LD running as few as 5-100 turns/day. Moreover, regression analysis showed that survivors in LL gained weight significantly faster than survivors in LD (significant difference in slopes, $p<0.05$), despite the fact that animals in LL ran more. Similarly, increased survival in LL was not due to increased food consumption. There was no difference in ad lib food consumption between rats in LL and LD, and both groups showed the same drop in food consumption at the beginning of food restriction. Food consumption in LD rats dropped below consumption in LL rats only during the last stages of activity-stress. Other measurements showed that drinking followed a pattern similar to the pattern seen in feeding. There were no significant differences between the two groups until the onset of the later stages of disease in the LD animals. Additional measurements also permit us to exclude the possibility that LL rats excreted less feces than rats in LD 12:12. There was no difference by weight in the fecal excretions of the two groups until the rats in LD entered the terminal stages of the syndrome. Then, rats in LD defecated less than rats in LL.

Despite our failure to detect any gross differences between the two groups that appeared before the onset of obvious pathological changes, we could not exclude the possibility that increased light exposure played some role in the beneficial effects of constant light. Consequently, we examined the effects of 27 hr days (LD 13.5:13.5) on activity-stress. In this experiment LD 13.5:13.5 was substituted for LL; this light schedule alters circadian organization but still provides the same (50%) overall time in

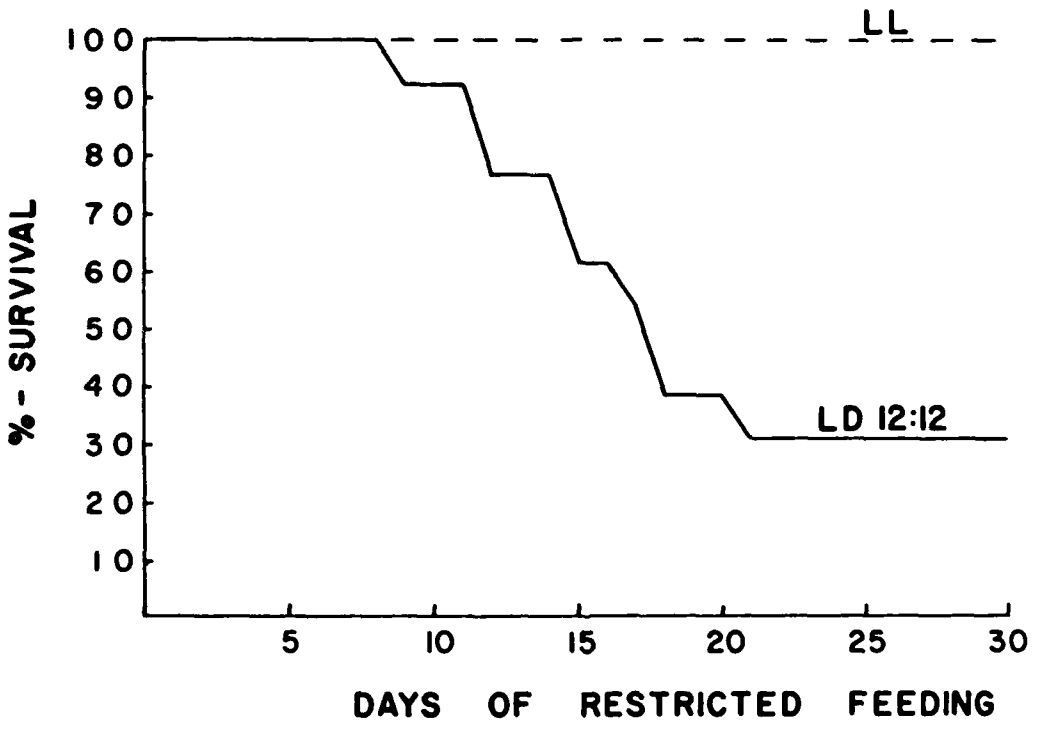


FIG 3

SURVIVAL OF ACTIVITY-STRESS RATS IN LL OR LD

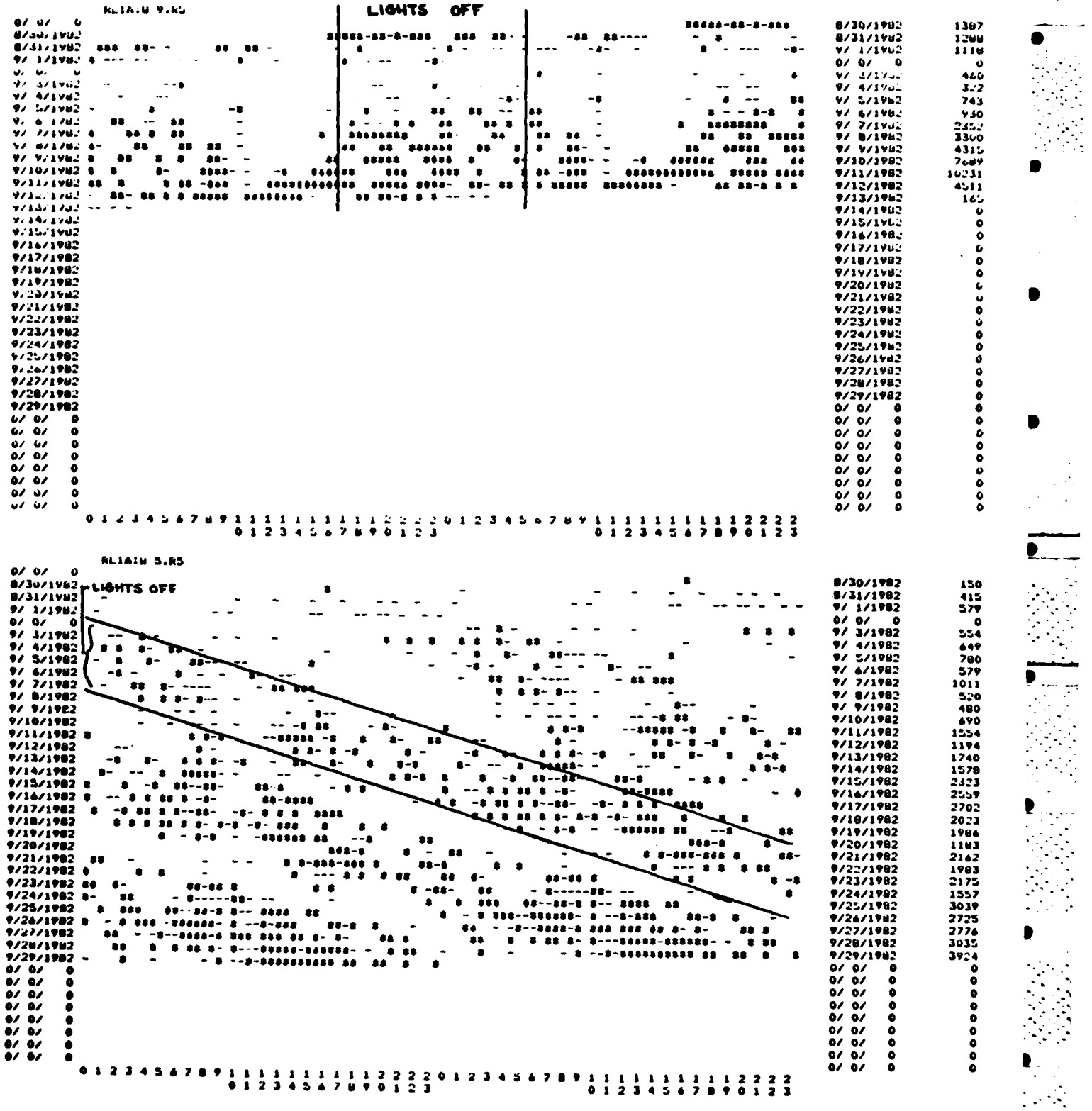
light as LD 12:12. We have done two separate experiments using this time schedule. Figure 4 shows teletype plots of wheel running from a rat in LD 12:12 and from a rat in LD 13.5:13.5. As before, data are double plotted, and the darker the symbol, the greater the number of wheel turns. The major difference between the two is that the plot from the rat in LD 13.5:13.5 is much longer than the plot from the rat in LD 12:12. This is because no 27 hr rat died while all of the 24 hr rats did. Here too there was no difference in the food or water consumption or the amount of running between the two groups until the final stages of activity-stress (from 9/10 until death for W9, the 12:12 rat). Thus, the beneficial effects of non-24 hr days are not due to differences in amount of light exposure across the experimental groups since they are still found when overall time in light is equated.

In the replication experiment, the same qualitative difference was found, but the protective effect was less marked. Of the 8 rats in each group, all 8 of the 24 hr rats died but only 5 of the 8 27 hr rats died. However, rats in 27 hr days lived significantly longer than rats in 24 hr days, and an examination of the rats' weights revealed that there was a significant difference in weight loss across the 2 conditions. Thus although there was not a significant difference in mortality, the non-24 hr schedule delayed both death and the onset of disease as manifested by weight loss. While we do not completely understand the reason for the quantitative differences between these 2 experiments, we believe that we may have found a seasonal effect on susceptibility to activity-stress. When we do our studies in the fall and winter, the differences between the 2 experimental groups is lessened; in contrast, the differences are magnified when the studies are done in spring and summer. In addition, some of our data suggest that during the fall and winter, rats in activity-stress may die earlier and at higher body weights. Such seasonal differences in disease susceptibility have been reported to occur in other stress models using rats (Wilson, 1971).

Most recently, we have studied the effects of constant dark (DD) on activity-stress. This is an important condition because DD seems to distort the circadian system much less than the other non-24 hr days that we have discussed. Rats in DD will continue to exhibit free-running rhythms for life. In LL, the rat's circadian rhythm eventually breaks down and disappears. Consequently, the original resonance notion that optimal environments encourage circadian periods near 24 hrs or near the free-running period would predict that 24 hr days and DD might have similar optimal effects. This prediction appears to be half right. DD and 24 hr days had similar effects on activity-stress. There were no differences between rats subjected to activity-stress in DD and 24 hr days in mortality, time to death, or any other measures. However, since other non-24 hr schedules mitigate the effects of activity-stress, this similarity hardly seems optimal. These observations have an additional significance, though. They show that not all non-24 hr days have beneficial effects, and therefore provide further motivation for mapping a range of schedules in an effort to understand the effects of circadian changes on disease susceptibility.

To summarize, constant light and 27 hr days protect rats from the consequences of the activity-stress paradigm that routinely occur during standard 24 hr days; constant dark, on the other hand, is not protective.

FIG. 4



TTY PLOTS OF WHEEL RUNNING FOR RAT IN
LD 12:12 (TOP) AND LD 13.5:13.5 (BOTTOM)

The protective effect may manifest itself on one of 3 levels -- either a difference in overall mortality, a difference in time to death or a difference in body weight of survivors. The hypothesis that we make from these data is that the protective effect may be a consequence of altering the organization of an animal's biological rhythms.

Spontaneous Disease and Non-24 Hr Schedules -- Cardiomyopathy Model: Our early observations suggesting that the circadian alterations produced by non-24 hr days might reduce disease susceptibility all involved stress induced disease models. In order to be sure that the beneficial effect of non-24 hr days were not restricted to stress-induced diseases, we needed to examine this phenomenon in a spontaneous disease. Consequently, we compared the course of disease in cardiomyopathic hamsters living in normal 24 hr days and in constant light (Tapp et al., 1983). Cardiomyopathic hamsters are an inbred strain with a genetically determined heart disease that results in heart failure and early death. Forty-one male, cardiomyopathic hamsters (BIO 14.6; Telaco, Bar Harbor, ME) were randomly assigned to live in either 24 hr days (LD 12:12) or in constant light (LL). In an attempt to further accelerate the course of their disease, we gave both groups 0.07% saline as drinking water; we recorded saline consumption. Body weights were recorded throughout the experiment in an attempt to follow the onset and progress of heart failure. Hamsters were weighed on a rotating schedule so that each hamster was weighed every third day. Upon death, hamsters were autopsied for gross signs of heart failure. Fluid in the abdominal and thoracic cavities was measured. The heart, lungs, liver, kidneys, and spleen were removed, weighed and examined for gross signs of congestion.

Hamsters living in constant light lived significantly longer (median=349 days) than hamsters living in 24 hr days (median=391 days) ($p < 0.001$) (see Figure 5). This difference amounted to a 10% increase in longevity for the hamsters living in constant light despite the fact that animals living in constant light actually drank more saline than animals living in 24 hr days. Furthermore, autopsy results showed that hamsters dying in LL had signs of significantly more severe heart failure than hamsters dying in LD 12:12. Thus, hamsters living in LL were able to survive more severe failure than hamsters in LD 12:12. These observations suggest that the therapeutic effects of altering an animal's circadian rhythms are not restricted to stress induced diseases. Living in non-24 hr days can retard the course of a spontaneously occurring heart disease.

Behavioral and Visceral Rhythms of Monkeys and Non-24 Hr Schedules: The results of our chronotherapy work led us to the hypothesis that the protective effects, reviewed above, were a consequence of some change in the organization of the animal's biological rhythms. Moreover, changes in temporal organization have been reported to produce marked behavioral effects. However, as we noted before, there is considerable confusion about the parameters of temporal organization that influence disease resistance and behavior. In fact, one change in temporal organization, internal desynchrony, is commonly invoked as an explanation for both beneficial and harmful effects. Consequently, we developed a system for studying behavior and temporal organization in monkeys. By providing a model for studying the effects of non-24 hr schedules on the biological rhythms and behavioral performance of an animal that is a close phylogenetic relative of man, we believe that we will have taken an important first step towards optimizing

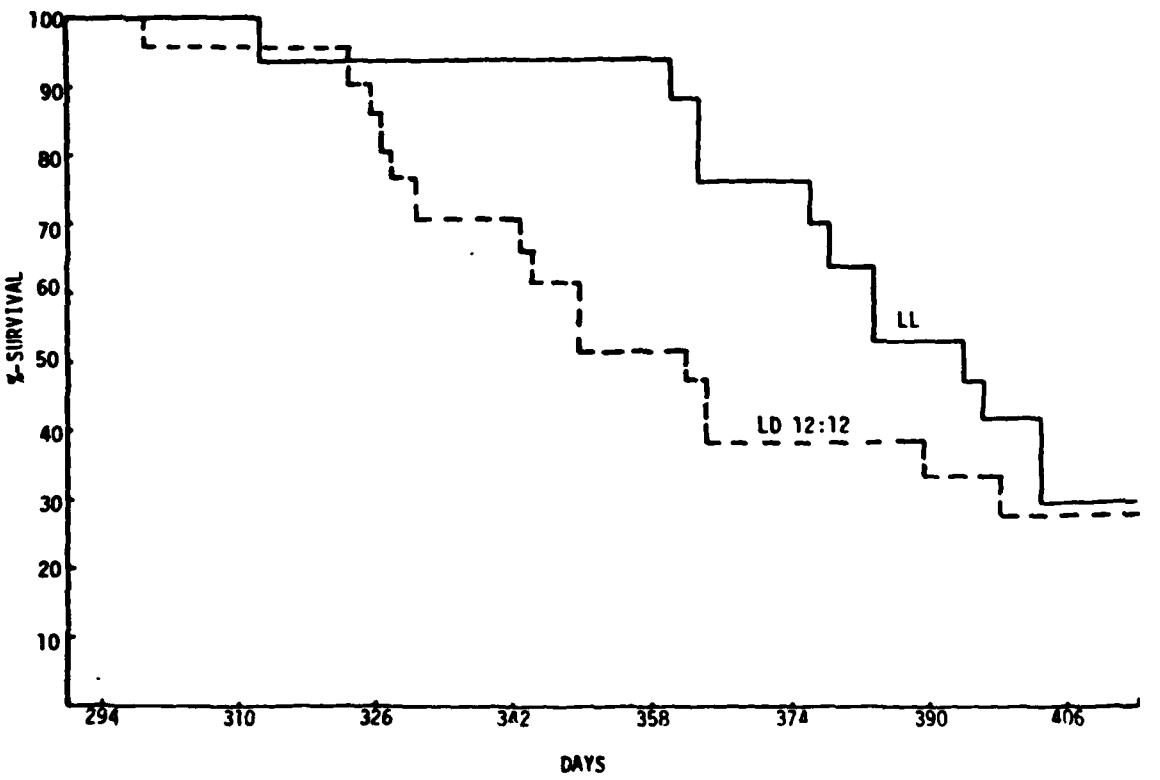


Fig. 5

SURVIVAL OF CARDIOMYOPATHIC HAMSTERS RAISED IN LL AND LD

the health and performance of people who must cope with nonstandard temporal environments.

The basic experiment examines the effects of entrainment schedules on two groups of monkeys: those with free access to food and those working on a sequential vigilance-discrimination task. The free feeding (FF) group enables us to investigate the effects of different entrainment schedules on the temporal organization of several biological rhythms within individual animals. The vigilance-discrimination performance of the Task Contingent (TC) group provides information about the effects of different entrainment schedules on the performance of behavioral tasks. Comparisons between the two groups enables us to evaluate the effects of task demands on biological rhythms and to evaluate any Task x Temporal schedule interactions.

Two rhythms, temperature and activity, are continuously monitored in all monkeys. These two rhythms were chosen because many reports suggest that they represent two circadian systems with different characteristics. They have also been the two systems most frequently observed to exhibit internal desynchronization (e.g., Wever, 1979; Moore-Ede et al., 1982). In addition, the cortisol rhythms of both groups will be monitored at different stages of the experiment. These three rhythms provide a basis for comparing biological rhythms of the free feeding (FF) monkeys and task contingent (TC) monkeys. In addition to the three common measures, we record the feeding patterns of FF monkeys and the vigilance-discrimination performance of TC monkeys.

The vigilance-discrimination task was chosen with several constraints in mind. The task had to extend over a considerable fraction of the day. It had to be paced so as to be amenable to time series analysis (i.e., reasonably uniform trial density over time), and it had to provide stable performance in well-trained animals so that learning could be eliminated as a potential confound. The current task meets these requirements, and it measures performance of tasks similar to those that have been sensitive to jet lag in humans.

Adult male rhesus monkeys are adapted to living in primate chairs. Free-feeding monkeys have constant access to a nose key which delivers Noyes 750 mg pellets on a fixed ratio schedule; the FR used is as low as needed to minimize pellet wastage. Task-dependent monkeys work for Noyes pellets on an 8 hr daily schedule (from 0900 to 1700 h during the initial LD 12:12 phase). Fixed to the chair in front of the monkey's hands are 3 levers. Fixed to the box at eye level is a Powell multiple cue light. A white light is illuminated on a VT 2.4 min schedule (i.e., stimuli are delivered at varying times but on the average once every 2.4 min). The monkey has 10 sec to press the middle lever. If this is done correctly, the white light goes off and either a red or a green light ($p = .5$ for each) comes on. The monkey then has 5 more sec to press the correct lever (i.e., right lever for red and left lever for green). A correct response is reinforced by a pellet and by turning the cue light off. If the vigilance task is missed, no discrimination trial is presented. If an error is made on the discrimination task (i.e., either waiting too long or pressing the wrong lever), no pellet is delivered and the cue lights are left on for the rest of the 5 sec period with levers inoperative. Figure 6 shows a portion of our graphic of one such session which is output daily as part of our computer's batch job.

FIL: BEING PROCESSED IS----RLOC:0925 .29

TIME	ERROR	GREEN	WHITE	RED	ERROR
1028			196	57	
1031		59	193		
1036		52	162		
1038			118	100	
1040			139	55	
1042			230	61	
1046		52	131		
1048		59	115		
1049		58	193		
1053		53	133		
1056			112	60	
1105			158	61	
1109			174	103	
1110			197	59	
1112			217	60	
1116		59	127		
1118		53	101		
1119		63	212		
1122			177	60	
1123		56	216		
1127		56	205		
1128			207	62	
1136		53	133		
1137			242	64	
1141			135	60	
1143		58	206		
1146		56	194		
1147			218	57	
1149		57	354		
1151			239	59	
1155			208	62	
1157		55	166		
1208		181	377		
1209			1000		
1210			216	60	
1211			244	56	
1214			213	56	
1216		52	225		
1217			167	64	
1219		58	283		

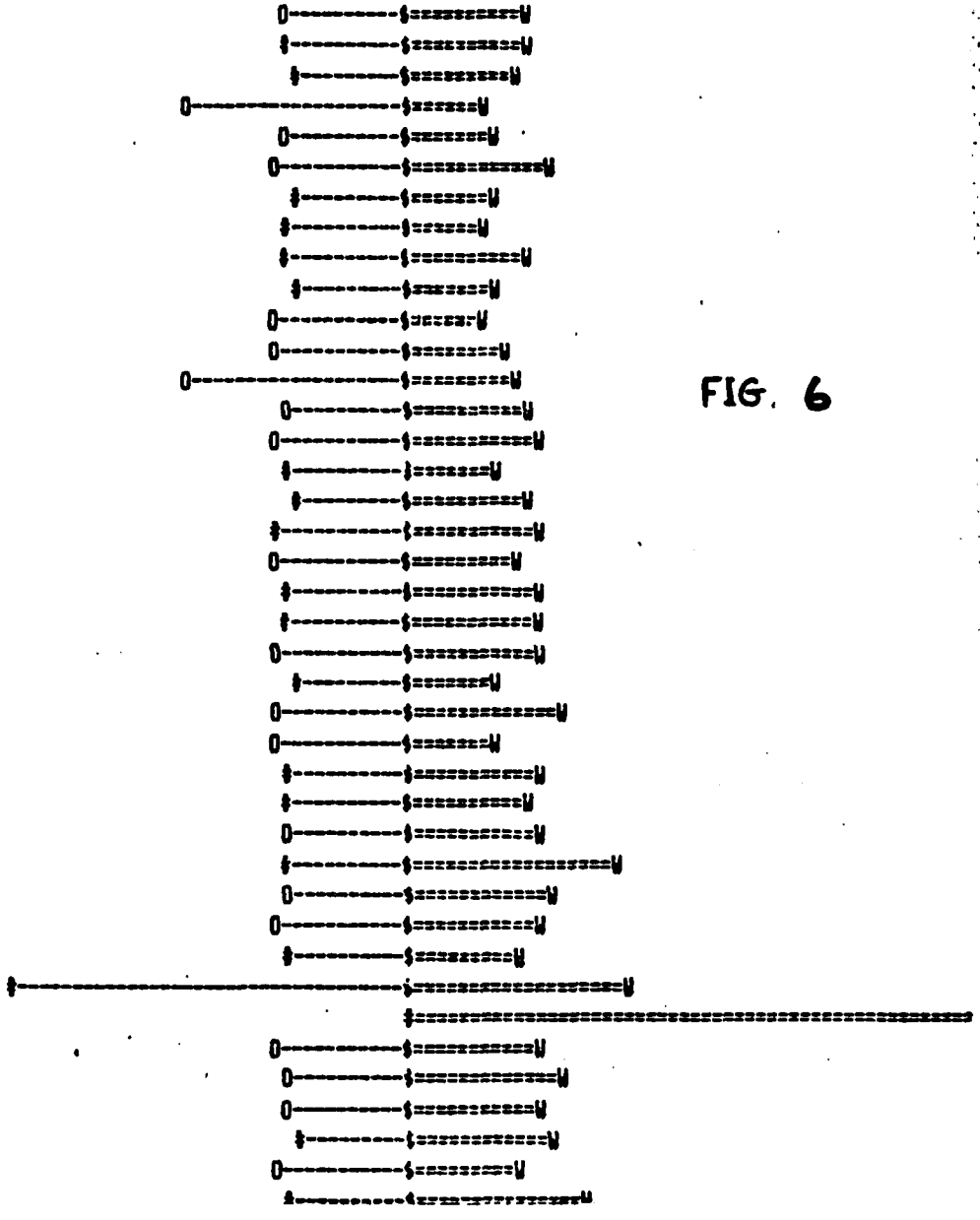


FIG. 6

TTY PLOT OF MONKEY VIGILANCE-CHOICE DATA FOR 1 DAY

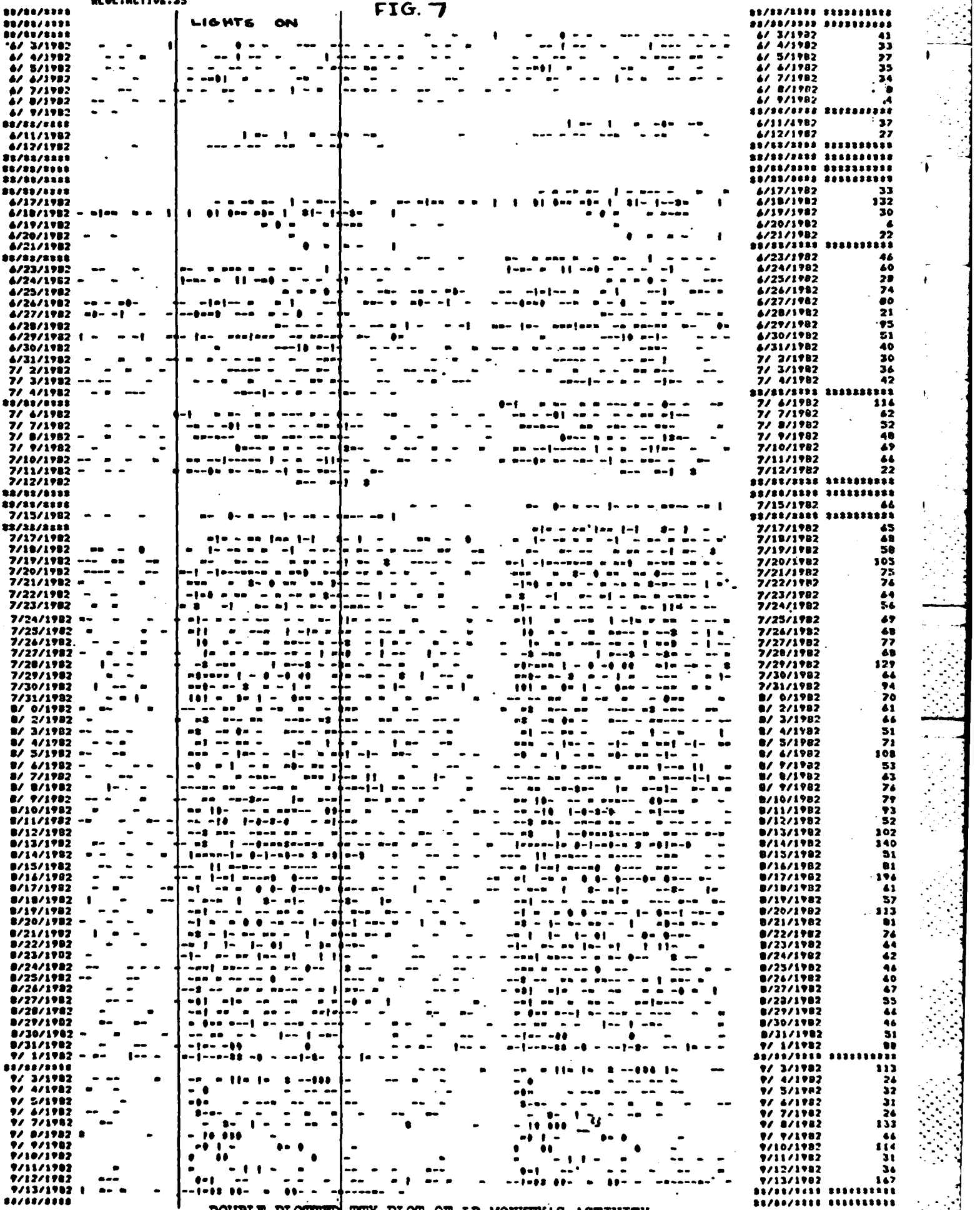
To the left are the numerical data, i.e., actual latencies in decisec. Thus, a count of 1000 in the column labelled WHITE means the monkey did not press the middle lever in 10 sec, while counts less than 1000 represent the number of clock ticks in the successful vigilance trial. If the white light was detected, the numbers in the rows labeled GREEN or RED list the latency of the press for the choice task in decisec. If a mistake was made, the latency of this response is printed out in the appropriate column labelled ERROR. This presentation allows us to check the actual numbers of the latencies. The righthand part of the figure depicts these numbers graphically. The bar on the right with the W on the end graphs the latencies of the vigilance task. Note that no data are plotted for the discrimination task on the vigilance trial with the very long latency; that is because the monkey did not detect the target in the time allowed. Note also that when latency criteria for the vigilance task are met, data are plotted for latency in the discrimination task on the left. A different symbol has been used to depict "red" choices and "green" choices. If a mistake is made (none occurred in the trials depicted in the figure), the latency is graphed as prolonged, and a different plotting symbol is used. As can be seen, fluctuations are easily seen for the vigilance task; since the differences in latencies in the discrimination task are in the range of just a few msec, fluctuations are not readily visible for this aspect of the task.

For chronic instrumentation, the chaired monkeys wear a loose fitting nylon dress which is attached to the chair's abdominal plate. The dress allows the animal to scratch its body but makes any instrumentation under the dress or below the abdominal plate inaccessible to the monkey's hands. This eliminates the need for a belt or a thoracic plate. To record activity, we have fitted a mercury switch potted in epoxy into one of the sleeves of the dress. The output of this switch is then fed through a SKED input into our computer. Figure 7 shows a teletype plot of one monkey's activity data. As can be seen, this monkey is entrained to an LD 12:12 schedule. The data are plotted in 30 min bins, but since they are collected in 10 min bins, the data are accessible for spectrum analysis at an adequate enough sensitivity to show ultradian rhythms of 20 min or more should they exist.

The monkeys have rectal temperature probes chronically inserted per anus. We have found that these are well tolerated and remain in place for long periods of time when the probe is stiffened slightly by placing a thin piece of wire along it within a length of protective heat-shrink tubing. Based on discussions with NP personnel, we chose a Baily instrument to interface to our computer. The noise in the thermometer is $\pm$ 0.1 ^{o}C. Since an A to D conversion step would have inserted another error of up to two times this instrument error, we elected to interface the thermometer to our computer via the thermometer's BCD output attached to our computer's parallel input. Figure 8 shows a teletype plot of one monkey's temperature data for a one week period of time. The sharp edge of the 24 hr temperature rhythm is readily apparent. Finally, after the administration of Ketamine anesthesia, each monkey is aseptically prepared with a chronic indwelling femoral vein catheter to allow us to sample blood for plasma cortisol every 15 min during a 10 hr period which surrounds the 8 hr work period with an hour on each end. It is important to note that the methods outlined above allow us to collect concurrent behavioral data (i.e., related to each of the 2 aspects of the task and to motor activity) as well as physiological data (i.e., core temperature and plasma cortisol). This has never been done before and

BLOCIACTIVE.3S

FIG. 7



DOUBLE PLOTTED TTY PLOT OF LD MONKEY'S ACTIVITY

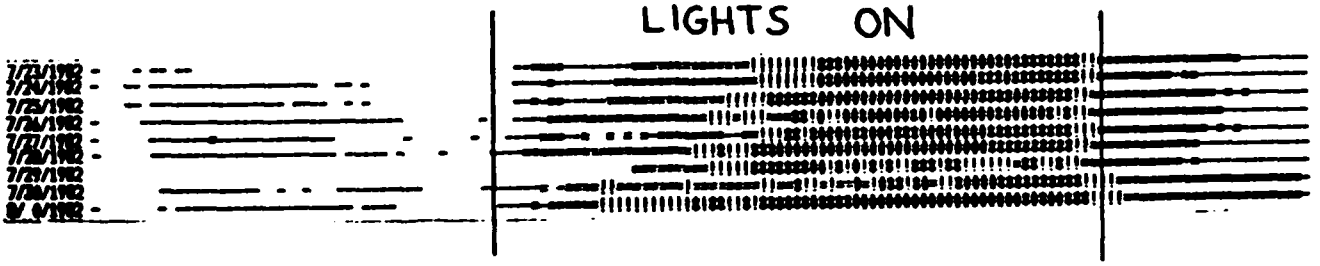


FIG. 8

SINGLE PLOTTED TTY PLOT OF
MONKEY'S RECTAL TEMPERATURE

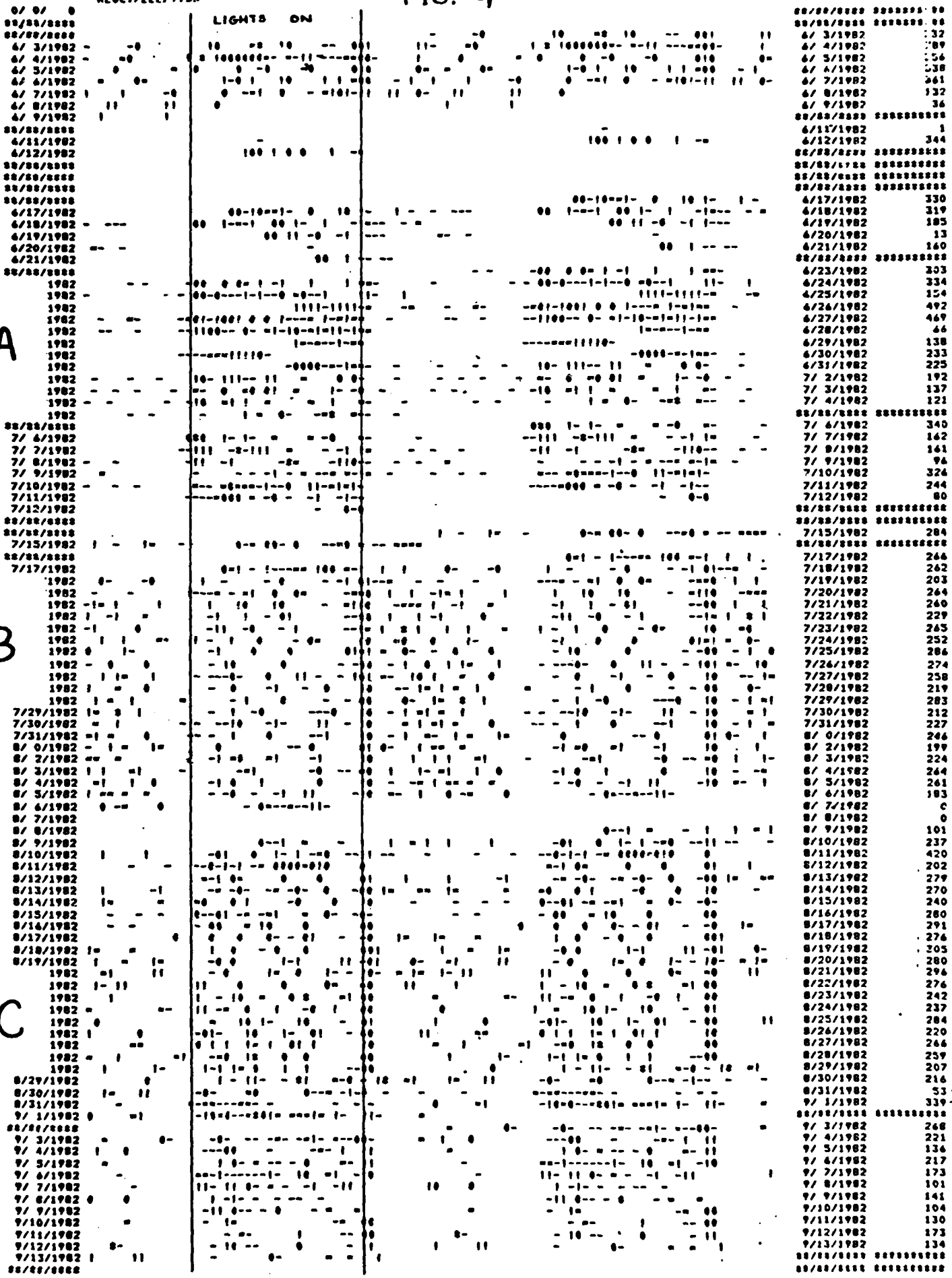
represents the methodological development which we plan to use in the continuation of this research in the future.

At present, we have collected data from monkeys in three entrainment conditions: LD 12:12, following a 6 hr phase advance (still ending in LD 12:12), and LL. Much of the data from these experiments remains to be analyzed, but a cautious presentation of the analyses performed to date seems reasonable and worthwhile. Although the interpretations of the data which follow apply to the figures accompanying them, the reader should understand that similar results have been observed in at least two additional monkeys.

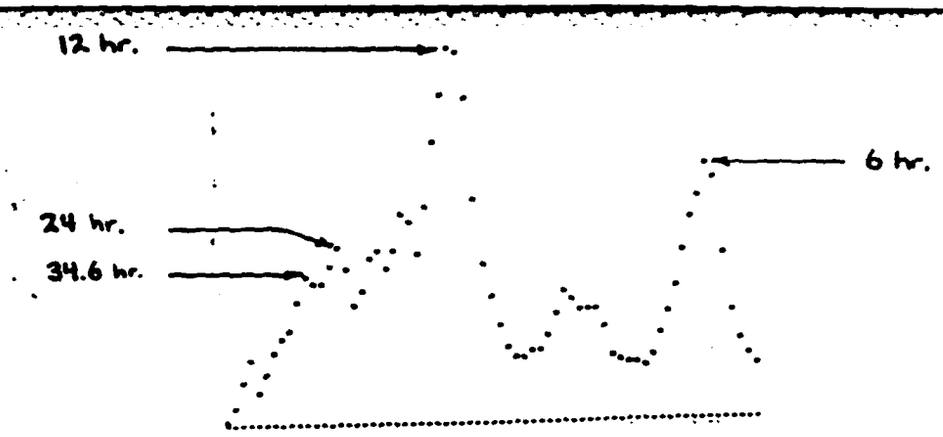
Figure 9 shows the feeding record of a monkey in the FF condition. As before, this record is double-plotted with a resolution of 30 min. Gaps in the record are due to occassional equipment failure. Vertical lines indicate the time of light onset and offset. Despite the early gaps in the record, it is easy to see that this monkey meets conventional criteria for entrainment from the beginning of the record. However, our interest in the fine structure of continuous behavioral performance led us to look closely at the fine structure of rhythms in the FF condition as well. The results were surprising. In section A of this record, note the alternation of periods when the monkey eats at night followed by periods of no nighttime eating. Spectrum analysis of this section of data (Figure 10) reveals the expected 24 hr period and an additional 34.1 hr component that matches graphical estimates of the low frequency component in this section; although of low power, this small peak was found consistently for all 3 monkeys. Since we see similar low frequency components in the feeding and/or activity records of most of our monkeys during the early phases of chair adaptation, we believe the data indicate that, as in other animals, monkey activity and feeding are comprised of more than one circadian oscillator. The low frequency components could then be explained as low frequency circadian components that are captured by the 24 hr light cycle more slowly than components nearer to 24 hrs.

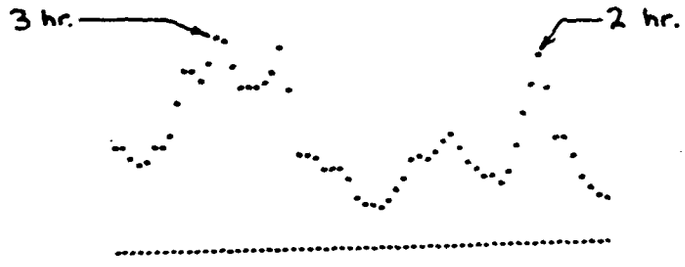
At present, these low frequency components are difficult to interpret. Similar findings in other systems are scanty, but many of the data analysis methods applied to these data would not detect these components. On the other hand, circadian systems with prominent low frequency components may be relatively rare. Indeed, to our knowledge, the only other well-documented examples of such low frequencies in mammals are those found in man. This comparison becomes all the more attractive in light of the observation that two monkeys in LL have shown brief, but clear, switches to circa-48 hr periods (6 cycles for one monkey and 11 cycles for the other). In fact, the monkey that switched for 11 cycles had previously shown an abrupt shift to a 48 hr activity period in the early stages of entrainment to LD 12:12. These long cycles were graphically obvious (see Figure 11) and confirmed by spectrum analysis, suggesting that the low frequency oscillator was able to entrain to the 24 hr light cycle by 1:2 frequency demultiplication (Wever, 1979). Behavioral periods in this range have been reported for humans free-running in constant conditions or in situations of failing entrainment (e.g., Wever, 1979), however, we have not been able to find a report of such long periods in an animal model. Thus, the rhesus circadian system may be organized more like the human systems than other known animal models.

FIG. 9



DOUBLE PLOTTED TTY PLOT OF LD MONKEY'S FEEDING





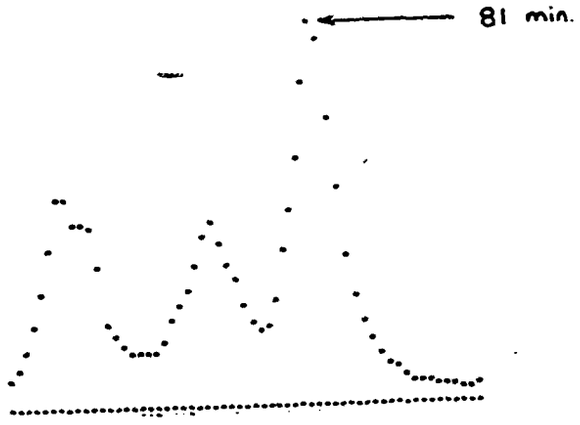
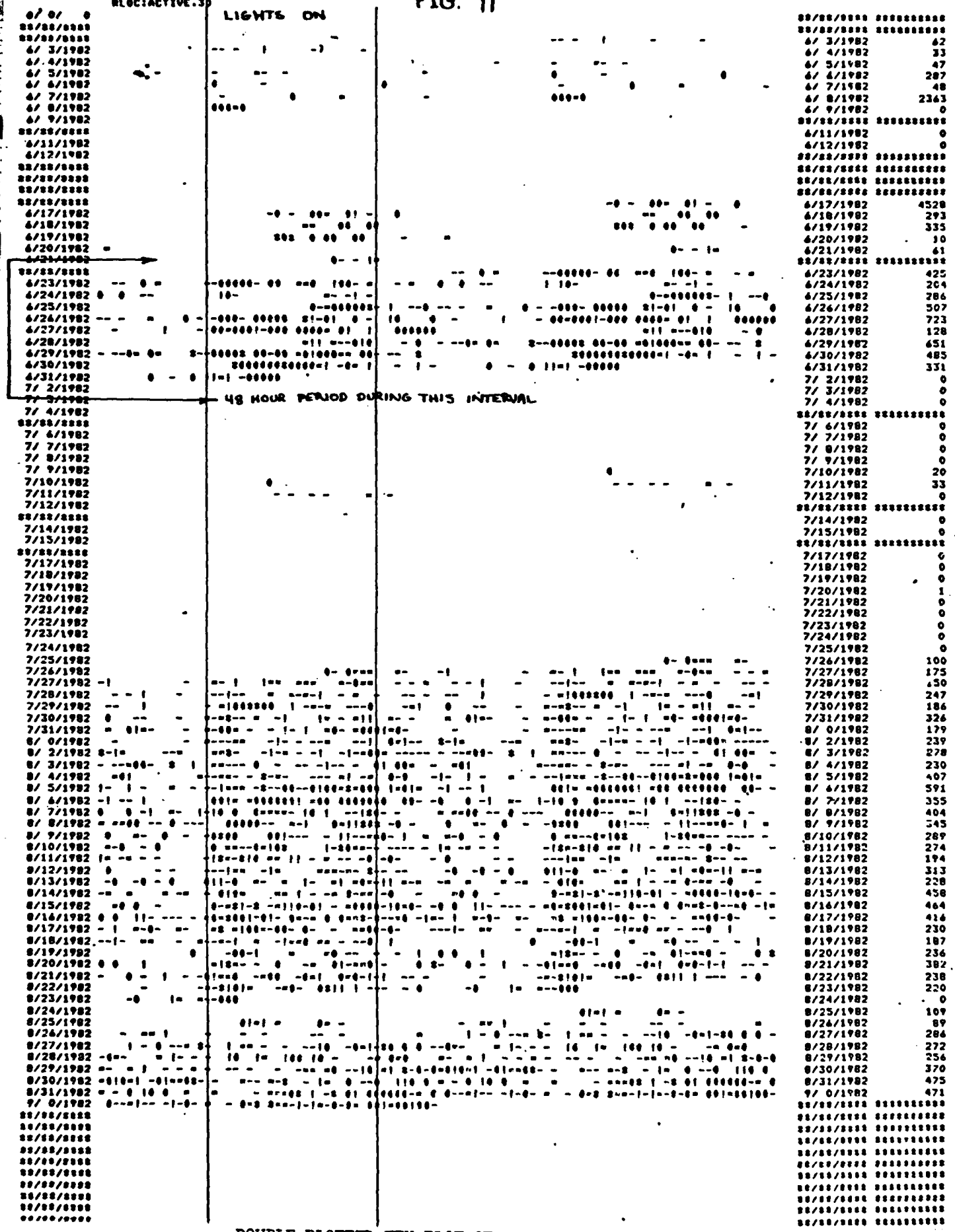


FIG. 10

SPECTRUM FROM SECTION A OF FIGURE 9

FIG. 11



DOUBLE PLOTTED TTY PLOT OF LD MONKEY'S ACTIVITY

Even within the day, feeding is not a continuous behavior. It is organized into short bouts with clear pauses between them. The pattern of the bouts provides the fine structure of the rhythm. The spectrum of section A reveals prominent 6 and 12 hr periodicities plus important contributions at 81 min and 41.2 min (see Figure 10). (The reader should note that since we do not have a high resolution plotter, each spectral output on our LA-120 is 14 pages long; thus, in order to allow the reader to see the peaks under discussion, we have provided data from only those spectral ordinates.)

This pattern does not persist, however. Section B of Figure 9 depicts two very obvious changes from the pattern seen in section A. First, the alternating pattern of night feeding has disappeared. The monkey almost always eats during the early part of night. Second, the monkey has developed a sharp anticipatory peak that begins in the hour before light offset. These changes are reflected in the spectrum (Figure 12) by the disappearance of the 34.1 hr period. The 34.1 hr component seems finally to have been captured by the light cycle, but its effect can still be seen in the strongly negative phase angle (onsets after lights on, offsets after lights off) that the animal maintains with respect to the light cycle. In general, relatively slow (low frequency) rhythms tend to lag the phase of the entraining cycle (Aschoff, 1981). These changes are associated with changes in the fine structure of the rhythm. Eating bouts are spread out at more uniform intervals. In the spectrum, the 6 and 12 hr components are replaced by 3 and 2 hr components, and components near 82 and 41 min remain surprisingly stable.

In section C of Figure 9, the bouts seem to become even more uniformly dispersed. Looking down the page, each bout looks almost like a single circadian rhythm that is slightly noisily entrained to 24 hrs. In the spectrum (Figure 13), this change is reflected as an increase in power at the 82 min and 42 min periodicities. This change in fine structure is accompanied by changes in the major circadian component. In section C, the circadian component adopts a more positive phase angle, so that the monkey begins feeding sooner after light onset and eats less in the night.

Examination of activity for this monkey (see Figure 7) shows essentially the same slow improvement in the entrainment that was seen in feeding. This improvement of entrainment seems to be composed of at least two processes: the capture of frequencies that are much longer than 24 hr by the light cycle and the redistribution of the bouts that comprise the fine ultradian structure of the rhythm. At this point, the relationship between the ultradian fine structure and the circadian rhythm is not at all clear. However, it is somewhat intuitively appealing to think of the changes in bout distribution as the monkey analogue of developing a routine. The fact that the routine appears to be ultradian and periodic or near-periodic reinforces suggestions that this frequency band may be functionally important.

In contrast to activity and feeding, temperature rhythms did not appear to show slow, progressive changes in entrainment. Figure 14 shows two temperature spectra from data collected over a month apart. For all practical purposes, these spectra are identical. (The reader should note that for these where a fine grained analysis is not necessary, we are providing compressed summary spectra where data are summed over 8 ordinates for each

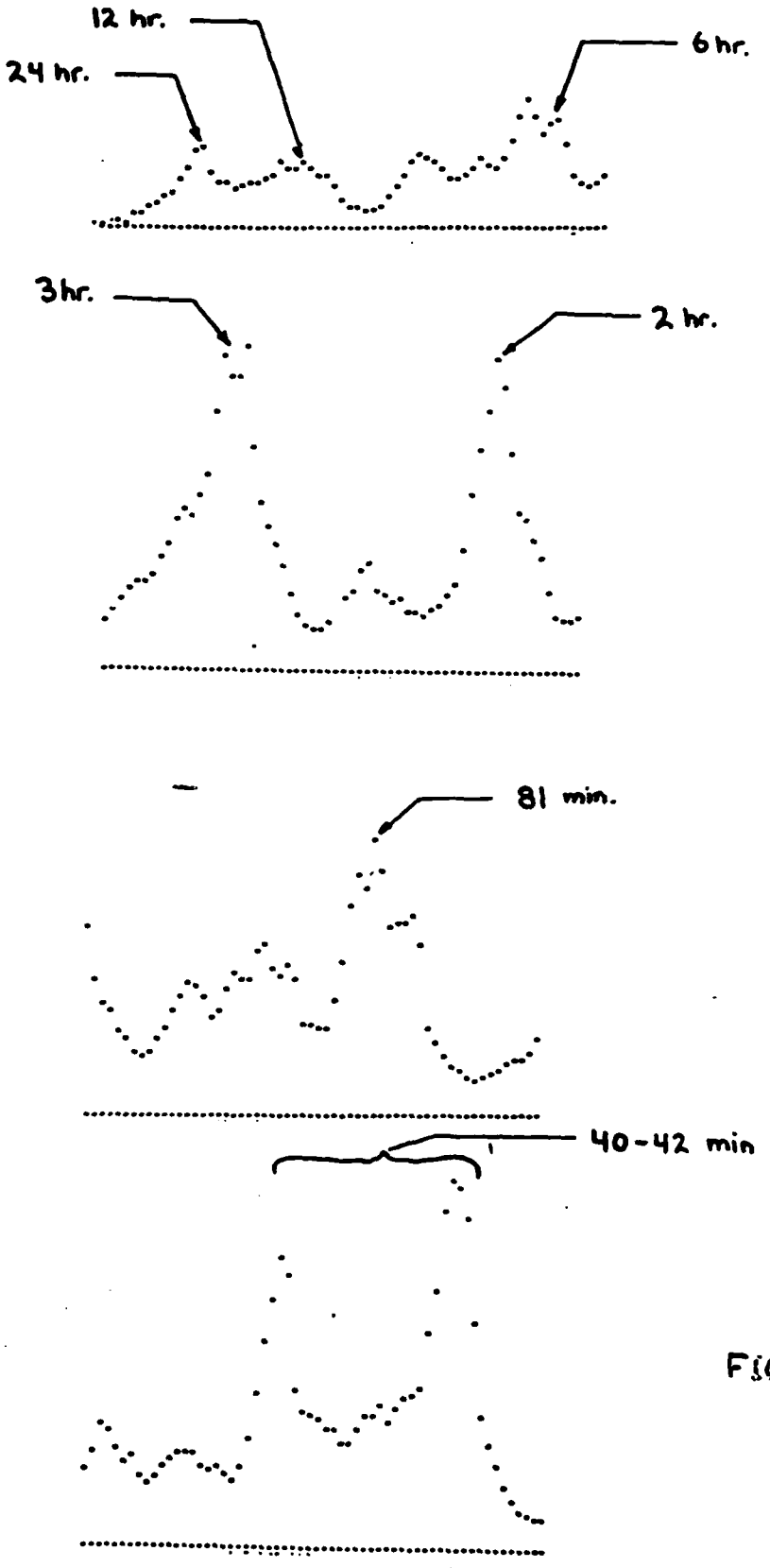


FIG. 12

SPECTRUM FROM SECTION B OF FIGURE 9

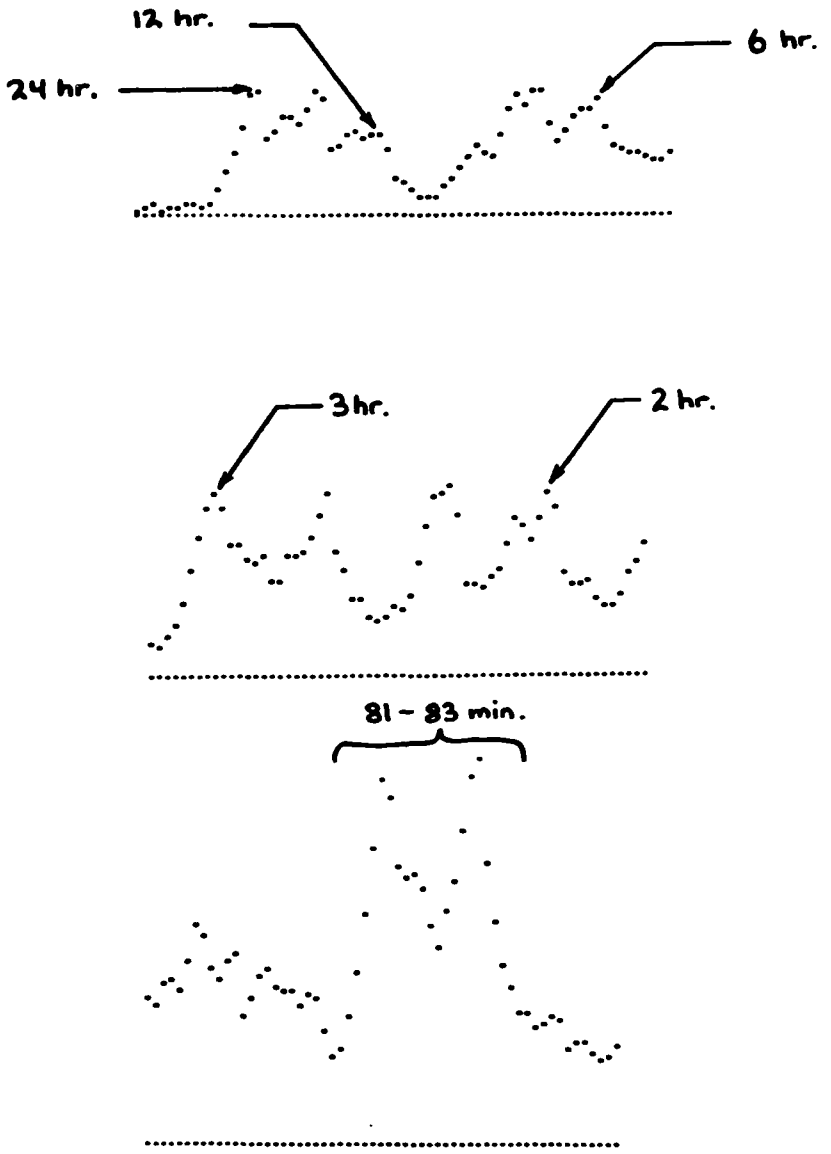


FIG. 13

SPECTRUM FROM SECTION C OF FIGURE 9

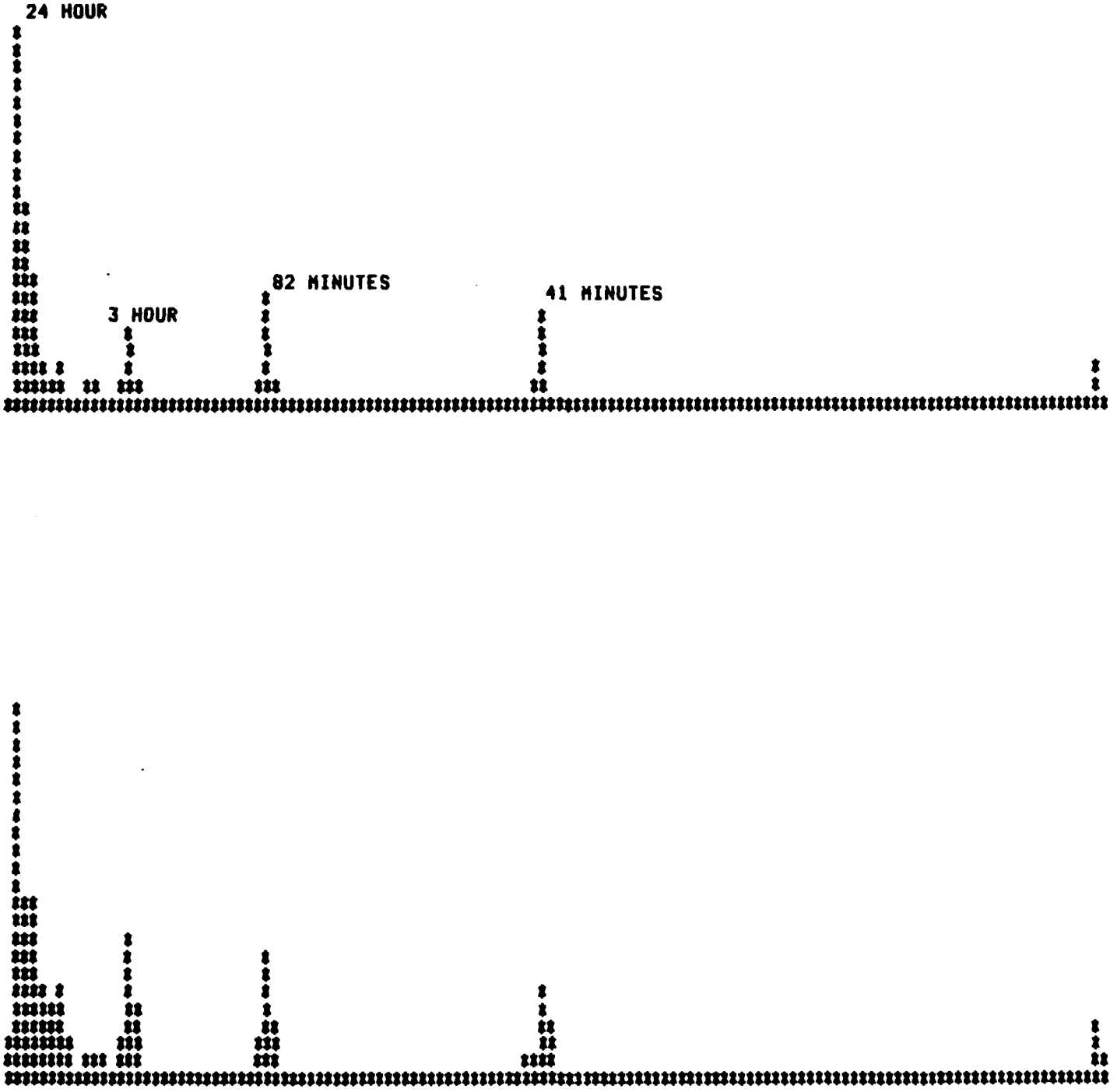


FIG 14

TEMPERATURE SPECTRA FROM A MONKEY

point graphed; although such depictions can produce some distortions of the real spectra, they facilitate visual examination of the entire spectrum.) These observations support the general consensus that temperature rhythms are more stable and regulated much more tightly than behavioral rhythms such as activity or feeding (Wever, 1979). Even the ultradian temperature rhythms were relatively tightly regulated, exhibiting stable components near 85 min and 42 min. This is particularly interesting because feeding and activity both exhibited stable ultradian components around 85 and 42 min that were stable over three months despite the changes in other frequencies. Others have suggested low frequency interactions between temperature rhythms and the sleep-wake cycle (Czeisler, et al., 1980), however, our data suggest that there may also be a high frequency ultradian interaction between temperature and behavioral rhythms such as activity and feeding.

The data above clearly indicate that it is time to reexamine the concepts of internal synchrony and desynchrony and their functional importance. Is an animal desynchronized when its temperature rhythm is stable and its behavioral rhythms are slowly changing their phase angle with respect to the light cycle? More importantly, if conventional entrainment to 24 hr days is this complicated, is it likely that we can describe the changes that are important for health and performance in non-24 hr days or other exotic schedules by dealing with only one frequency in one rhythm. We think not. Consequently, in the new project we will continue mapping the relationships between different rhythms across a broad range of frequencies, and we will investigate the relationships between low and high frequency rhythms.

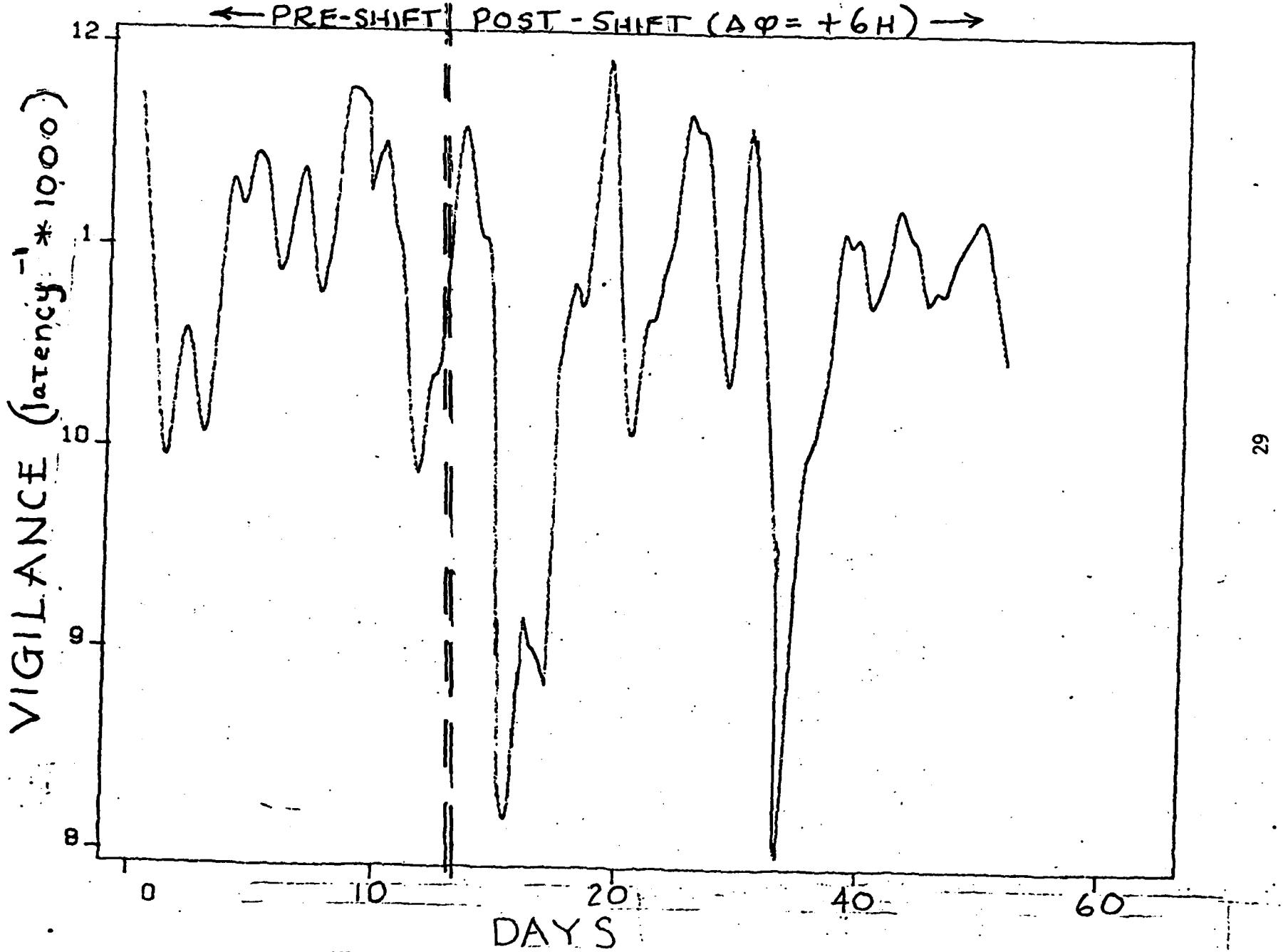
Examination of the performance data from monkeys in the vigilance-discrimination task revealed that baseline performance in 24 hr days is essentially asymptotic and stable. (As with data from the FF monkeys, all substantive comments which follow are based on consistent findings for a group of 3 monkeys). Preliminary analyses revealed no systematic effects of intertrial interval on vigilance or discrimination, and no consistent relationship between vigilance performance and subsequent discrimination performance. There was however, a relationship between time of day and both vigilance and discrimination performance. Further work is required to determine if this relationship reflects a biological rhythm, or whether there is any relationship between performance and any of the other variables we are measuring.

We have recently drawn cortisol samples from our first monkey working on the task, but they have not yet been analyzed.

Figure 15a shows the vigilance performance of a TC monkey. In this graph, speed of performance has been plotted as 1000/latency to respond. Thus, peaks on the graph correspond to peaks in performance, and troughs correspond to impaired performance. For display purposes, the data have been smoothed using Cleveland's (1978) LOWESS procedure to facilitate inspection of the changes in overall performance across days. All statistics however, were computed on the raw speed (1000/latency) data. As the plot shows, performance prior to the phase shift fluctuated around a stable overall level. Shortly after the 6 hr phase shift, however, the monkey's vigilance performance dropped sharply and significantly ($p < 0.001$). Over the next 5 days, though, the monkey's performance recovered to pre-shift levels. Allowing for task differences and other pertinent factors, this period of impairment and recovery corresponds reasonably well with the time course of jet lag in

FIG 15A

FILE - TASK. 34



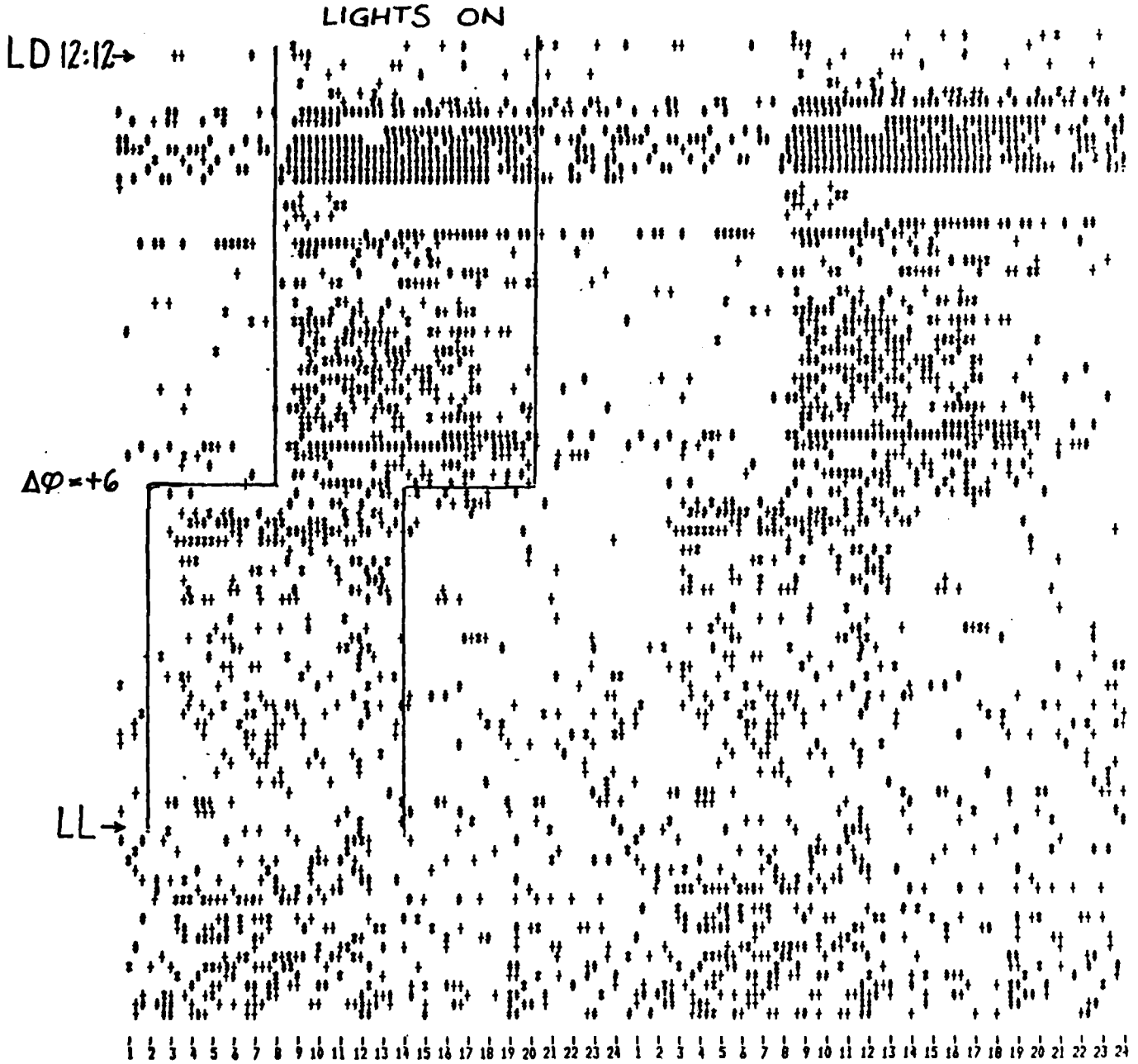
MONKEY VIGILANCE BEHAVIOR BEFORE AND AFTER PHASE SHIFT

humans (see Graeber, 1982 for a recent summary). These observations are encouraging. They suggest that in the monkey vigilance-discrimination model, phase shifts produce behavioral impairments similar to those found in human jet lag. The second large trough in performance following the phase shift may prove to be equally interesting, though. During that trough, the performance impairment is as great as the immediate post-shift impairment, even though the second trough occurs days after the animal appears to have regained pre-shift performance levels. Following the data beyond the scope of this graph shows at least three additional cycles of good performance interrupted by significant periods of impaired performance. We have seen similar cycles of good performance interrupted by spans of poor performance in all TC monkeys following phase shift. At present, we do not understand the mechanism of these cycles. However, they suggest that an individual may suffer periods of impaired performance weeks after their apparent recovery from the effects of a phase shift. If this is true of humans, it would have obvious practical importance.

Figure 15b shows activity from a monkey in the vigilance-discrimination task from before the 6 hr phase advance through the time of the monkey's release into LL. Lines indicate times of light onset and light offset. Visual examination and time series analysis of this record shows that activity begins to respond to the new light cycle on the day of the shift, and within 3 days the circadian activity rhythm has reentrained to the new schedule. In contrast, the temperature rhythm of the monkey (Figure 16) reentrains much more slowly, requiring an average of 13 days to reach stability at the new phase. A similar difference in the rates of reentrainment of temperature and activity rhythms is typical of humans (e.g. Wever, 1979), suggesting again that the rhesus model may be a valuable model for studying the relationships between performance and temporal organization in different entrainment regimes.

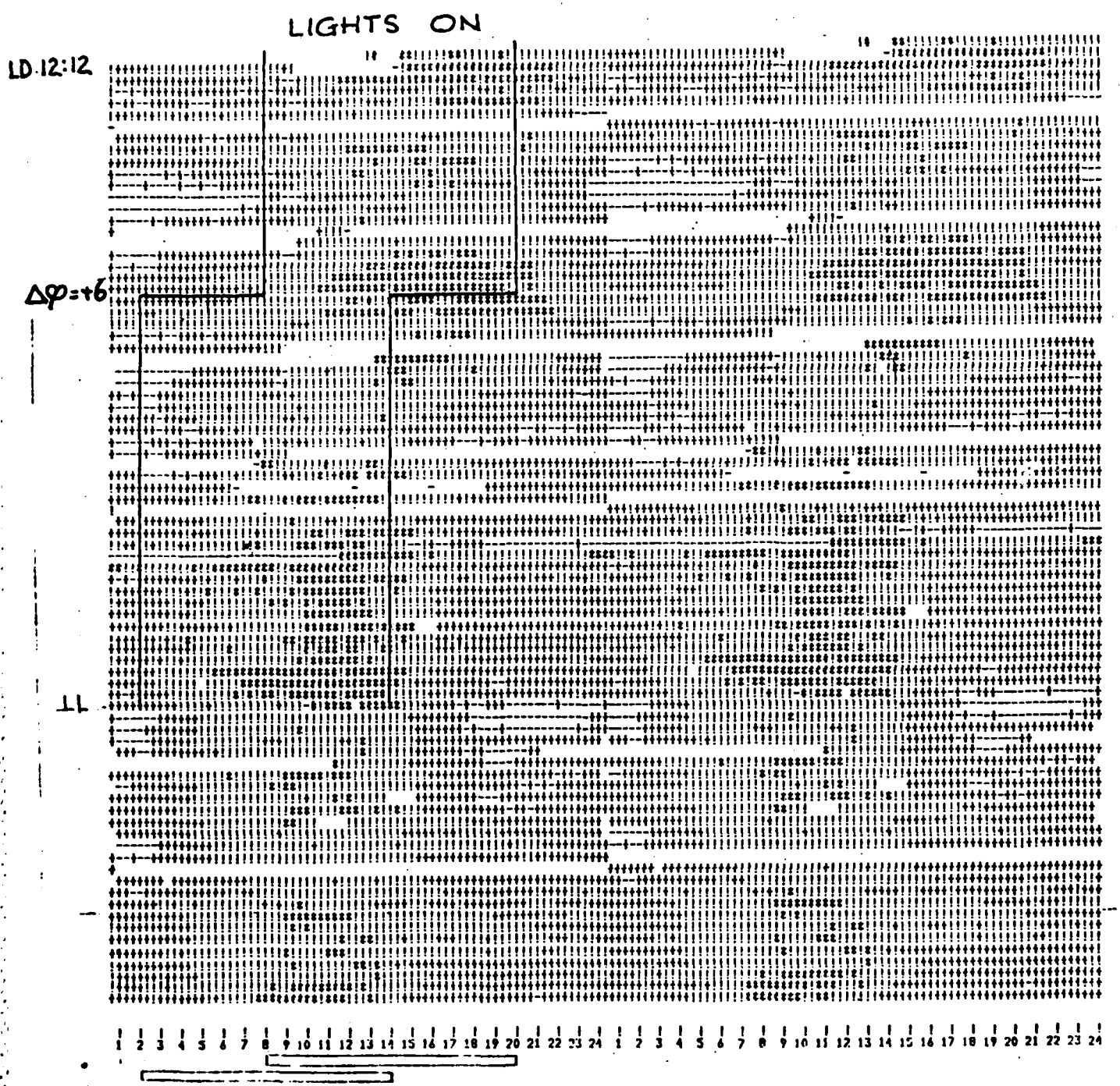
To summarize our progress to date, the FF experiments have produced surprising evidence of slow changes in the rhythm during conventional laboratory entrainment to LD 12:12. These changes appear to be comprised of at least 2 sorts of changes in the substructure of the rhythm: (a) low frequency components that can run independently of the main part of the observable circadian rhythm and (b) changes in the distribution of high frequency ultradian components. The importance of these substructural characteristics in describing internal temporal organization is emphasized by the fact that changes in circadian parameters such as phase angle or duration of alpha coincide with changes in low or high frequency components of the rhythm's substructure, suggesting that substructural parameters are intimately related to the conventional descriptors of circadian rhythms, such as phase shift or duration of alpha. Of course, these relationships need to be examined in constant conditions, in the absence of potential masking agents. Still, these findings suggest that it is not enough to talk about rhythms being internally synchronized or desynchronized. They suggest that it time to review and refine the ways that we describe internal temporal organization. Such refinements are a continuing part of this project's effort to determine the functional effects of changes in internal temporal organization. In addition, FF monkeys have shown circa-48 hr periods under free-running conditions in LL (and in one case in LD 12:12). This similarity with humans was surprising, but it suggests that the rhesus may indeed be a very good animal model of many aspects of the human circadi-

FIG 15B



MONKEY ACTIVITY BEFORE AND AFTER PHASE SHIFT

FIG. 16



MONKEY TEMPERATURE BEFORE AND AFTER PHASE SHIFT

an system. The TC experiments have shown that acute phase shifts can impair vigilance-discrimination performance in rhesus monkeys much like the impairments seen in human jet lag. This suggests that the rhesus vigilance-discrimination model may be a useful, cost-effective way to explore the effects of environmental time schedules on biological rhythms and behavioral performance in humans.

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PUBLICATIONS SUPPORTED BY CONTRACT:

Tapp, W. N. and Natelson, B.H. "Constant light reduces stress-induced disease." Fed. Proc. 40: 292, 1982.

Tapp, W., Ferrara-Ryan, M. and Natelson, B.H. "Circadian manipulations alter the course of heart failure in cardiomyopathic hamsters." Pavlovian Journal of Biological Sciences 18: 107, 1983.

Natelson, B., Ferrara-Ryan and Tapp, W. "Sex-related increase in stress ulcer disease in rats relates to hypothermia." Fed. Proc. 42: 754, 1983.

PERSONNEL RECEIVING CONTRACT SUPPORT INCLUDES:

Debra Creighton

Gerry Curtis

Charles Nary

Walter Tapp

BACK COVER

END

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